OBSTETRICS

Maternal plasma angiogenic index-1 (placental growth factor/soluble vascular endothelial growth factor receptor-1) is a biomarker for the burden of placental lesions consistent with uteroplacental underperfusion: a longitudinal case-cohort study

Steven J. Korzeniewski, PhD; Roberto Romero, MD, DMedSci; Tinnakorn Chaiworapongsa, MD; Piya Chaemsaithong, MD; Chong Jai Kim, MD, PhD; Yeon Mee Kim, MD, PhD; Jung-Sun Kim, MD, PhD; Bo Hyun Yoon, MD, PhD; Sonia S. Hassan, MD; Lami Yeo, MD

BACKGROUND: Placental lesions consistent with maternal vascular underperfusion (MVU) are thought to be pathogenically linked to preeclampsia, small-for-gestational-age newborns, fetal death, and spontaneous preterm labor and delivery; yet, these lesions cannot be diagnosed antenatally. We previously reported that patients with such conditions and lesions have an abnormal profile of the angiogenic placental growth factor (PlGF) and antiangiogenic factors (eg, soluble vascular endothelial growth factor receptor [sVEGFR]-1).

OBJECTIVE: The objectives of this study were to: (1) examine the relationship between the maternal plasma PlGF/sVEGFR-1 concentration ratio (referred to herein as angiogenic index-1) and the burden of histologic placental features consistent with MVU; and (2) test the hypothesis that angiogenic index-1 can identify patients in the midtrimester who are destined to deliver before 34 weeks of gestation with multiple (ie, ≥3) histologic placental features consistent with MVU.

STUDY DESIGN: A 2-stage case-cohort sampling strategy was used to select participants from among 4006 women with singleton gestations enrolled from 2006 through 2010 in a longitudinal study. Maternal plasma angiogenic index-1 ratios were determined using enzyme-linked immunosorbent assays. Placentas underwent histologic examination according to standardized protocols by experienced pediatric pathologists who were blinded to clinical diagnoses and pregnancy outcomes. The diagnosis of lesions consistent with MVU was made using criteria proposed by the Perinatal Section of the Society for Pediatric Pathology. Weighted analyses were performed to reflect the parent cohort; "n*" is used to reflect weighted frequencies.

RESULTS: (1) Angiogenic index-1 (PlGF/sVEGFR-1) concentration ratios were determined in 7560 plasma samples collected from 1499 study participants; (2) the prevalence of lesions consistent with MVU was 21% (n* = 833.9/3904) and 27% (n* = 11.4/42.7) of women with ≥3 MVU lesions delivered before 34 weeks of gestation; (3) a low angiogenic index-1 (<2.5th quantile for gestational age) in maternal plasma samples obtained within 48 hours of delivery had a sensitivity of 73% (n* = 8.3/11.4; 95% confidence interval [CI], 47–98%), a specificity of 94% (n* = 3130.9/3316.2; 95% CI, 94–95%), a positive likelihood ratio of 12.2, and a negative likelihood ratio of 0.29 in the identification of patients who delivered placentas with ≥3 MVU lesions at <34 weeks; (4) prospectively, at 20-23 weeks of gestation, a maternal plasma concentration of angiogenic index-1 <2.5th quantile identified 70% (n* = 7.2/10.3; 95% CI, 42–98%) of patients who delivered placentas with ≥3 MVU lesions before 34 weeks (specificity, 97% [n* = 2831.3/2918; 95% CI, 96–98%]; positive likelihood ratio, 23; negative likelihood ratio, 0.31); and (5) among women without obstetrical complications who delivered at term, angiogenic index-1 was lower in women with than without placental lesions consistent with MVU ($P < .05$).

CONCLUSION: Maternal plasma angiogenic index-1 (PlGF/sVEGFR-1) is the first biomarker for the burden of placental lesions consistent with MVU. We propose that an accumulation of these lesions in placentas delivered before 34 weeks is a histologic counterpart of an antiangiogenic profile.

Key words: acute atherosis, basal plate, fetal death, intervillous fibrin, persistent muscularization of the arteries, placental pathology, preeclampsia, preterm delivery, small for gestational age, soluble Flt-1, syncytial knot, villous infarction

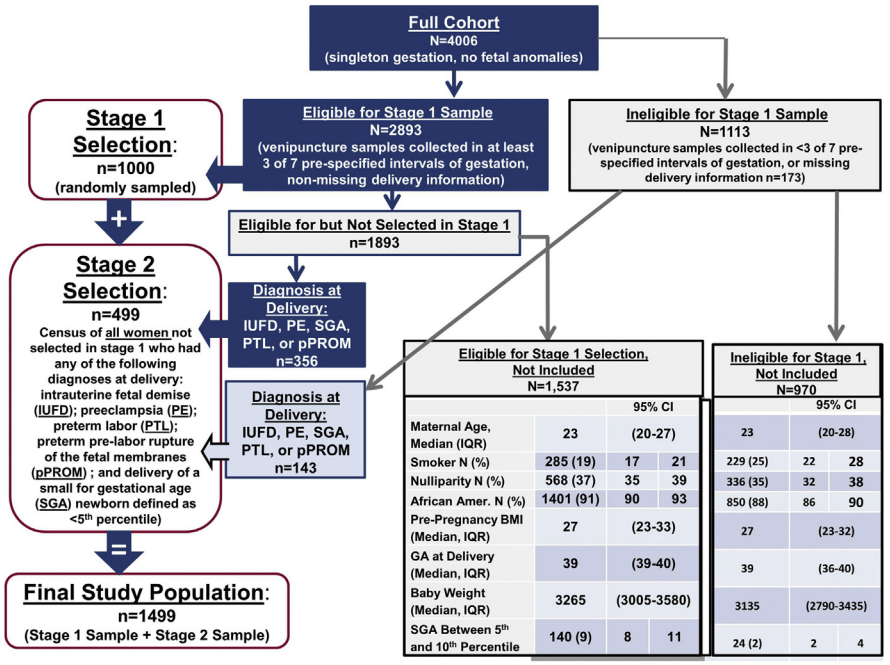
Introduction

The uteroplacental circulation is established around the end of the first trimester.[1-14] Physiologic transformation of the spiral arteries increases the size of these vessels, allowing blood to flow into the intervillous space,[15-22] where oxygen and nutrients are transported to the fetus.[23-26] Disruption of maternal vascular development is thought to result in reduced blood supply to the placenta. Histologic placental features consistent with maternal vascular underperfusion (MVU) are associated with preeclampsia,[27-55] intrauterine growth restriction,[35,50,56-67] fetal death,[50,68-81] and delivery of small-for-gestational-age (SGA) newborns.[81-83] These conditions contribute to a substantial fraction of perinatal morbidity and mortality, often mediated by indicated preterm delivery.[84-87] Uteroplacental vasculopathy is also associated with spontaneous preterm

Cite this article as: Korzeniewski SJ, Romero R, Chaiworapongsa T, et al. Maternal plasma angiogenic index-1 (placental growth factor/soluble vascular endothelial growth factor receptor-1) is a biomarker for the burden of placental lesions consistent with uteroplacental underperfusion: a longitudinal case-cohort study. Am J Obstet Gynecol 2016;214:629.e1-17.

0002-9378/$36.00
Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ajog.2015.11.015

FIGURE 1
Flow diagram describing selection of participants



Flow diagram describing 2-stage selection of study participants.

BMI, body mass index; *CI*, confidence interval; *IQR*, interquartile range.

Korzeniewski et al. Biomarkers of maternal vasculopathy. Am J Obstet Gynecol 2016.

labor (PTL) with intact membranes and preterm prelabor rupture of membranes (pPROM)[50,88-92]; thus, maternal vascular obstructive lesions, bleeding/vessel integrity, and lack of physiologic conversion of maternal spiral arteries might constitute or interact in pathways to spontaneous as well as indicated preterm delivery,[93] possibly contributing to an even larger fraction of adverse pregnancy outcomes.[94] Indeed, we propose that processes resulting in maternal vascular lesions contribute to many of the "great obstetrical syndromes."[22,95,96]

Our group has demonstrated that an imbalance in maternal plasma concentrations of the angiogenic placental growth factor (PlGF) and antiangiogenic factors (eg, soluble vascular endothelial growth factor receptor [sVEGFR]-1) is characteristic of a large fraction of women who have or will develop preeclampsia.[44,97-111] We have also found significant differences in angiogenic and antiangiogenic factor distributions among women with uncomplicated pregnancies and those who are or will be affected by spontaneous PTL with intact membranes,[112] fetal death,[109,113,114] massive perivillous fibrin deposition,[115] twin-to-twin transfusion syndrome,[116] and delivery of SGA newborns.[103,117,118] Moreover, we have reported that differences in angiogenic and antiangiogenic factor concentrations are greater when patients with these obstetrical syndromes have placental lesions consistent with MVU.[44,109,111] Therefore, we hypothesize that the ratio of angiogenic to antiangiogenic factor concentrations in maternal plasma reflects the burden of lesions consistent with MVU.

The objectives of this study were to: (1) examine the relationship between the maternal plasma PlGF/sVEGFR-1 concentration ratio (referred to herein as angiogenic index-1) and the burden of histologic placental features consistent with MVU, irrespective of clinical diagnosis; and (2) test the hypothesis that angiogenic index-1 can identify patients in the midtrimester who are destined to deliver before 34 weeks of gestation with multiple (ie, ≥3) histologic placental features consistent with MVU.

Materials and Methods

Study design and participants

A 2-stage case-cohort[119] sampling strategy was used to select participants into this prospective nested longitudinal case-cohort study from among 4006 women with singleton gestations. These women, who had been enrolled between 6-22 weeks of gestation at Hutzel Women's Hospital, Detroit, MI, from 2006 through 2010, were followed up until delivery. Exclusion criteria were multiple gestations and any of the following at enrollment: active vaginal bleeding, obstetrical complications, serious medical illness (renal insufficiency, congestive heart disease, and chronic respiratory insufficiency), chronic hypertension requiring medication, asthma requiring systemic steroids, requirement of antiplatelet or nonsteroidal antiinflammatory drugs, active hepatitis, or fetal anomalies.

Figure 1 describes the selection of study participants. In the first sampling stage, 1000 women were randomly selected from among 2893 who had venipuncture samples collected in at least 3 of 7 predefined gestational age intervals (8-15.9, 16-19.9, 20-23.9, 24-27.9, 28-31.9, 32-36.9 and ≥37 weeks). In the second sampling stage, all remaining women who had any of the following diagnoses at delivery were selected from among the 3006 women who were not selected in the first stage of sampling: preeclampsia, PTL, fetal death, pPROM, and delivery of a newborn weighing <5th centile for gestational age.[120] The most centrally located venipuncture sample within each of the 7 intervals defined by gestational age for each patient was used for analysis, and in cases of a tie, the first sample obtained was selected.

All patients provided written informed consent, and the use of clinical data and biological specimens for research purposes was approved by the Institutional Review Boards of Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development,

Download English Version:

https://daneshyari.com/en/article/6144032

Download Persian Version:

https://daneshyari.com/article/6144032

Daneshyari.com